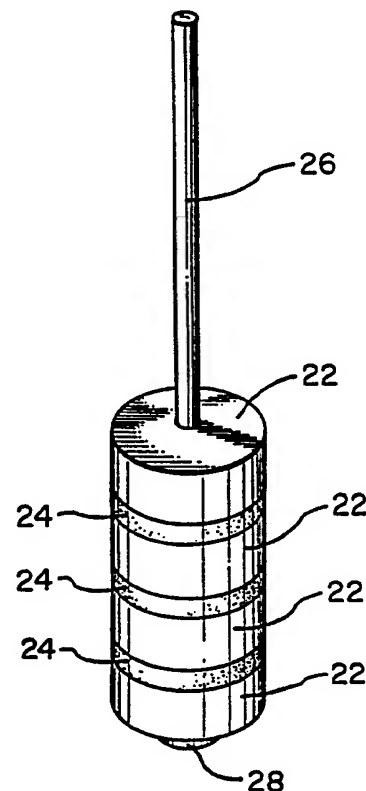




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 9/68	A1	(11) International Publication Number: WO 91/03237 (43) International Publication Date: 21 March 1991 (21.03.91)
(21) International Application Number: PCT/US90/04384 (22) International Filing Date: 3 August 1990 (03.08.90) (30) Priority data: 403,751 5 September 1989 (05.09.89) US (71) Applicant: UNIVERSITY OF UTAH RESEARCH FOUNDATION [US/US]; University of Utah, 210 Park Building, Salt Lake City, UT 84112 (US). (72) Inventors: STANLEY, Theodore, H. ; 4800 Oak Terrace Drive, Salt Lake City, UT 84124 (US). HAGUE, Brian ; 4478 South Hawarden Drive, West Valley City, UT 84119 (US).		(74) Agents: NYDEGGER, Rick, D. et al.; Workman, Nydegger & Jensen, 1000 Eagle Gate Tower, 60 East South Temple, Salt Lake City, UT 84111 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: COMPOSITIONS AND METHODS OF MANUFACTURE OF ORAL DISSOLVABLE MEDICAMENTS (57) Abstract Dosage form and method of manufacture for producing a medicament capable of absorption through mucosal tissues. The drug (24) is to be incorporated into a dissolvable matrix (22). An appliance or holder (26) is attached to the dissolvable matrix (22) and mounted or sealed against button (28).		



DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Monaco
AU	Australia	FI	Finland	MG	Madagascar
BB	Barbados	FR	France	ML	Mali
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Fasso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GR	Greece	NL	Netherlands
BJ	Benin	HU	Hungary	NO	Norway
BR	Brazil	IT	Italy	PL	Poland
CA	Canada	JP	Japan	RO	Romania
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
DE	Germany	LU	Luxembourg	TD	Chad
DK	Denmark			TG	Togo
				US	United States of America

1

**COMPOSITIONS AND METHODS OF MANUFACTURE
OF ORAL DISSOLVABLE MEDICAMENTS**

BACKGROUND

5

1. The Field of the Invention

The present invention relates to compositions and methods of manufacture of oral dissolvable matrixes for medicaments used in the buccal, sublingual, pharyngeal, and esophageal transmucosal delivery of the medicaments. More particularly, the present invention is directed to compositions, and methods and apparatus for producing such compositions, for noninvasive administration of dose-to-effect amounts of medicaments through the mucosal tissues of the mouth, pharynx, and esophagus.

15

2. The Background of the Invention

Recently, numerous advancements have taken place in the field of pharmacology and pharmaceuticals with respect to the administration of drugs to treat various conditions. Despite the tremendous advancements in the field, however, drugs continue to be administered using substantially the same techniques that have been used for many decades. The vast majority of pharmaceutical agents continue to be administered either orally or by injection. Nevertheless, it is frequently found in the art that neither of these administration routes are effective in all cases, and both administration routes suffer from several disadvantages.

25

Oral administration is probably the most prevalent method of administering pharmacological medicaments. The medicament is generally incorporated into a tablet, capsule, or a liquid base, and then swallowed. The oral administration modality is often preferred because of its convenience. In addition, oral administration is generally

30

35

1 nonthreatening, painless, and simple to accomplish for most patients.

Nevertheless, oral administration of drugs suffers from several disadvantages. One disadvantage is that
5 pediatric and geriatric patients frequently have difficulty swallowing pills and other solid dosage-forms, and such patients often refuse to cooperate in swallowing a liquid medication. In addition, for many medicaments, the act of
10 swallowing the medicament often requires fluids and increases gastric volume and the likelihood of nausea and vomiting.

A further problem with oral administration is that the rate of absorption of the drug into the bloodstream after swallowing varies from patient to patient. The absorption
15 of the drug is dependent upon the movement of the drug from the stomach to the small and large intestines and the effects of secretions from these organs and on the resulting pH within the stomach and intestines. Anxiety and stress can dramatically reduce these movements and
20 secretions, prevent or reduce the final effects of the drug, and delay onset of the drug's effects.

Most significant is the fact that there is normally a substantial delay between the time of oral administration and the time that the therapeutic effect of the drug
25 begins. As mentioned above, the drug must pass through the gastrointestinal system in order to enter the bloodstream; this typically takes forty-five minutes or longer. As mentioned above, anxiety and stress often increase this delay.

30 For many applications, such as premedication before surgery or where immediate relief from pain or a serious medical condition or immediate effectiveness of the drug is required, this delay is unacceptable. In modern outpatient units and operating rooms where rapid turnover of patients

1 is essential for cost containment, extensive delays in the
action of a drug are simply unacceptable.

2 An additional disadvantage of oral administration is
3 that many drugs almost immediately experience metabolism or
4 inactivation. The veins from the stomach and the small and
5 large intestines pass directly through the liver. Thus,
6 drugs entering the bloodstream must first pass through the
7 liver before distribution into the general blood
8 circulation. More than sixty percent of most drugs (and
9 essentially one hundred percent of certain drugs) are
10 removed from the patient's bloodstream during this "first
11 pass" through the liver. The result is that oral
12 administration is impractical for many drugs, particularly
13 many central nervous system and many cardiovascular-acting
14 drugs that are used for rapid onset in critical care
15 situations, as a premedication prior to surgery, or for the
induction of anesthesia.

16 Further, additional stress is placed on the liver as
17 it removes the excess drug from the bloodstream. This is
18 particularly severe if the drug treatment has been
19 occurring over an extended period of time. The liver may
20 become overloaded with the drug's metabolite which then
must be excreted. As a result, there is an increased risk
of hepatic or renal disorders.

21 Another difficulty encountered in administering drugs
22 orally is that dosages are prepared or determined for use
23 with an "average" patient. Most drugs have widely varying
24 effects on different patients. These effects depend upon
25 patient habits, subtle genetic differences between
26 patients, blood volumes, age, and numerous other known and
27 unknown factors. Introducing a bolus of drug orally does
28 not provide the ability to control the precise dose needed
29 to obtain the desired effect, rather the dose is estimated
30 in order to produce an average effect in an average
31

1 patient. The result may be underdosing or overdosing a
particular patient.

Underdosing a patient because of a low susceptibility
to the drug fails to evoke the response sought by the
5 physician. Overdosing the patient can result in dangerous
depression of vital body functions, especially the heart
and lungs. This can cause prolonged respiratory depression
(necessitating mechanical ventilation after surgery),
cardiac depression, and cardiac arrest.

10 In order to avoid some of the disadvantages of oral
administration, injection is frequently used. Injecting a
drug (generally intravenously or intramuscularly), results
in rapid entry of the drug into the patient's bloodstream.
In addition, this type of delivery avoids the removal of
15 large quantities of the drug by the patient's liver. As a
result, less total drug is usually needed compared to
orally administered drugs. The drug instead becomes
rapidly distributed to various portions of the patient's
body before exposure to the liver.

20 Most patients, particularly children and geriatric
adults, have an aversion to injections. In some patients,
this aversion may be so pronounced as to make the use of
injections a serious concern. Since intense psychological
stress can exacerbate a patient's debilitated condition, it
25 sometimes becomes undesirable to use injections where the
patient is seriously ill or suffers from a debilitating
condition or injury.

In addition, individual variations in susceptibility
in the metabolism of various drugs (particularly drugs with
30 central nervous system activity) are even more profound
when utilizing the injection route. In many instances to
prevent overdosing, it is the practice to inject a patient
with a lower than average dose and then supplement the dose
with additional injections as necessary. This "titration"

1 makes necessary the use of repeated injections, which in
turn greatly increases stress on the patient. Again, a
precise dose cannot be administered to produce a precise
effect because the patient's response varies widely
5 depending on the specific characteristics of the specific
patient.

One common approach to preparing a patient for surgery
is to orally administer a sedative or anxiolytic. Although
quick onset of sedation or anxiolysis has not always been
10 a critical factor, it is more so now. Changing practices,
including the increased use of outpatient units for day
surgery and the pressures for cost containment in modern
medicine, dictate rapid onset of action and the use of an
absolutely ideal dose in order to avoid increased costs of
15 caring for patients with delayed recovery secondary to
slightly overdosing with anesthesia. Effective oral
administration of premedication drugs with central nervous
system activity (which cause a rapid onset of sedation and
anxiolysis without producing excessive sedation) is often
20 difficult to accomplish.

Some investigators have suggested that it may be
possible to administer medication through the buccal mucosa
of the cheek pouch or by sublingual administration. See,
U.S. Patent No. 4,671,953 entitled "METHODS AND
25 COMPOSITIONS FOR NONINVASIVE ADMINISTRATION OF SEDATIVES,
ANALGESICS, AND ANESTHETICS." Such administration through
the mucosal tissues of the mouth, pharynx, and esophagus of
therapeutic drugs possesses a distinct usefulness. Admin-
istration of drugs by this route does not expose the drug
30 to the gastric and intestinal digestive juices. In
addition, the drugs largely bypass the liver on the first
pass through the body, thereby avoiding additional meta-
bolism and/or inactivation of the drug.

1 Generally the drugs which are administered by any of
the methods described above have an unpleasant taste. As
a result, in order to allow for buccal or sublingual
administration through the oral mucosal tissues, it is also
5 necessary to incorporate the drug into some type of
pleasant tasting mass, such as a "candy" matrix.

 In the manufacture of medicated candy products by
existing methods, the therapeutic agent is added to a
molten candy mass. The resultant mixture is then
10 thoroughly mixed to ensure proper distribution of the drug
within the molten candy mass. The mixture is then poured
into a mold cavity while still molten and allowed to
solidify into a solid mass. Alternatively, the hot candy
mass may be poured into molds, the size and shape of which
15 may be determined as desired.

 For effective application of the drug, the final candy
product may contain the drug uniformly distributed
throughout in order to ensure uniform levels of medication.
Alternatively, for some applications, varying concentra-
20 tions within known and controlled ranges may be desired to
vary the rate of drug administration. Difficulties are
encountered in attempting to blend solid drugs in a uniform
or otherwise carefully controlled manner. Many drugs are
insoluble, or only partially soluble, in one or more of the
25 ingredients of the hard candy base. Thus, the resultant
product is often found to be lacking in uniform or
controlled distribution of the drug.

 In addition, it is often found that when the
temperature of the candy mass is increased in order to
30 enable a more uniform distribution (generally to a
temperature above approximately 230°C), considerable
decomposition of the drug takes place. While the extent of
decomposition may vary, high temperatures are generally
undesirable in the handling and processing of medications.

1 Thus, the process of formation of the candy product may
itself degrade and/or inactivate the therapeutic agent.

Furthermore, many presently available medicated candy
lozenges tend to crumble when placed in the mouth. As a
5 result, uniform release of the drug into the mucosal
tissues does not take place. Rather, the crumbled lozenge
is mostly chewed, and swallowed, and the drug enters the
bloodstream through the stomach and intestines as described
above. Thus, it will be appreciated that candy lozenges
10 have very definite limitations for use in the administra-
tion of a drug through the oral mucosal tissues. As a
result, lozenges have not been used to administer potent,
fast-acting drugs, such as drugs that affect the central
nervous system, the cardiovascular system, or the renal
15 vascular system.

While the administration of certain drugs through the
oral mucosal tissues has shown promise, development of a
fully acceptable method for producing a medication in a
desirable form and administering the medication has been
20 elusive. It has not been possible to develop an acceptable
candy product for use with most drugs without heating the
product to the point where degradation will be expected.

It should also be noted that pH conditions within the
mouth may tend to adversely affect the administration of
25 certain lipophilic drugs by the mucosal administration
route. It has been found in the art that administration of
drugs through the mucosal tissues generally occurs best
when the drug is in the unionized form. Variations in pH
affect the percentage of the drug which is unionized at a
30 particular point in time. As a result, the pH conditions
within the mouth can limit the effectiveness of certain
drugs administered buccally or sublingually in that those
conditions cause the drug to exist in the ionized form

1 which is largely unavailable for transfer across the
mucosal tissues.

Other potent drugs are substantially nonlipophilic and
do not naturally permeate mucosal tissues. Hence it would
5 be a significant advancement in the art of administering
potent, fast-acting drugs, if suitable methods and
compositions permitted both lipophilic and nonlipophilic
drugs to be administered transmucosally.

It would be another important advancement in the art
10 of administering potent, fast-acting drugs, if suitable
methods and compositions provided a precise dosage to a
precise effect in every patient. A related advancement in
the art would be to provide such methods and compositions
that avoid the disadvantages of overdosing, underdosing,
15 and the immediate metabolism encountered in the "first pass
effect," yet do not involve injection by needle into the
patient.

It would be a further significant advancement in the
art to provide methods and compositions for incorporating
20 drugs (including insoluble drugs) into a soluble matrix
without heating the mixture to the point that degradation
occurs. It would be a related advancement in the art to
provide such a method which provided the capability of
uniformly incorporating insoluble drugs into the soluble
25 matrix.

Such compositions and methods of manufacture are
disclosed and claimed herein.

BRIEF SUMMARY OF THE INVENTION

30 The present invention relates to compositions and
methods of manufacture for producing medicament
compositions for use in administering potent, fast-acting
drugs transmucosally. Furthermore, the present invention
relates to such compositions and methods which are useful
35

1 in administering drugs in a dose-to-effect manner such that
sufficient drug is administered to produce precisely the
desired effect. The invention also relates to a manufac-
5 turing technique that enables both lipophilic and nonlipo-
philic therapeutic agents to be incorporated into a
flavored dissolvable matrix material and to attach the
matrix mixture onto an appliance or holder. In use, the
present invention provides for the administration of drugs
10 through the mucosal tissue of the mouth, pharynx, and
esophagus, thereby avoiding the problems of both injection
and oral administration.

Employing the present invention, the drug may be
introduced into the patient's bloodstream almost as fast as
through injection, and much faster than using the oral
15 administration route, while avoiding the negative aspects
of both methods. A dosage-form within the scope of the
present invention can be used to administer drugs in a
dose-to-effect manner, or until the precise desired effect
is achieved.

20 The present invention achieves these advantages by
incorporating the drug into a dissolvable matrix material.
The dissolvable matrix may include carbohydrates, fats,
proteins, waxes (natural and synthetic), hydrocarbons, and
other materials which safely dissolve in the mouth. The
25 dissolvable matrix, or dosage-form, can be used to
administer drugs in a dose-to-effect manner, or until the
precise desired effect is achieved. The dosage-form
preferably has an appliance or handle attached thereto to
permit removal from the patient's mouth.

30 The manufacturing methods of the present invention
overcome many of the limitations previously encountered in
forming a medicated lozenge. The present invention teaches
the combination of ingredients by geometric dilution. That
is, the two smallest ingredients by weight are first

1 thoroughly mixed, then the next smallest ingredient or
ingredients by weight equal to the weight of the previous
ingredients is added and is thoroughly mixed with the
existing mixture. This procedure is repeated until all of
5 the components, including the desired therapeutic agents,
are fully combined.

After mixing, the mixture may be compressed, poured
into a mold cavity, dehydrated, freeze dried, or otherwise
formed as an integral drug delivery system. In some
10 embodiments within the scope of the present invention,
specific confectionery components are combined in order for
the mixture to form an integral solid mass. These
components may include, for example, compressible
confectioner's sugar, sorbitol, mannitol, and maltodextrin.

15 In other embodiments within the scope of the present
invention, certain fats, waxes, or hydrocarbons may be
combined with the desired therapeutic agent and compressed
to form a dissolvable drug delivery system. Sugars and
other carbohydrates, flavors, dyes, mold releasing agents,
20 binding agents, and flavor modifiers may also be combined
with the dissolvable matrix material and therapeutic agent
before being compressed.

In yet other embodiments within the scope of the
present invention, therapeutic agents may be combined with
25 hydrogels or gelatins to form a dissolvable drug delivery
system.

These embodiments overcome many of the problems of the
prior art. According to the present invention, insoluble
drugs can be added to the matrix without the necessity of
30 attempting to dissolve the drug. In addition, the high
temperatures, which are generally required to form a molten
candy matrix of the prior art and which can cause
degradation of some drugs, are avoided using the present
invention. Therefore, even drugs with relatively low

1 melting points or those drugs which can experience
decomposition below their melting points, can be
incorporated into a dissolvable dosage-form.

5 A further advantage of the present invention is that
flavoring problems are overcome in many cases. Flexibility
in adding flavors is provided in that solubility of the
components is not required in order to incorporate any
particular flavor into the matrix. Thus, flavorings,
10 drugs, and other components (which may be insoluble in
liquid form) are easily mixed when they exist as a dry
powder.

Buffering agents and other types of pH control can
also be added simultaneously in order to provide for
maximum drug efficiency. It will be appreciated that drugs
15 in the unionized form are more readily transported across
the mucosal membrane. Therefore, if pH conditions can be
adjusted to maximize the percentage of unionized drug
available, the effectiveness of the drug is maximized.

Buffering agents are particularly important for those
20 drugs that partially ionize within the pH range of the
mouth, such as weak acid and weak base drugs. Generally,
buffering agents are more important when hydrophilic drugs
are used because those drugs usually have lower mucosal
permeability and dissolve more readily in saliva within the
25 mouth.

Permeation enhancers may also be incorporated within
the dissolvable matrix to improve the permeability of the
mucosal membrane. The permeability of both lipophilic and
nonlipophilic drugs may be improved by using suitable
30 permeation enhancers.

Various dosage-form configurations are also possible
employing the present invention. For example, layers of
drug may be interspersed between layers of a dissolvable
composition. Since the present invention teaches the use

1 of different dissolvable matrix materials which can be
compressed, poured, dried, or otherwise formed into a solid
dosage-form, virtually any desired type of mold can be used
for the formation of the dosage-form.

5 It may also be desirable to incorporate a handle or
holder in the dissolvable matrix material as the matrix is
being formed. Alternatively, the handle may be glued to
the matrix material by a dissolvable bonding agent, such as
confectioner's glue, once the dissolvable matrix is formed.
10 The handle provides for easy removal of the dissolvable
matrix from the mouth of the patient once the desired
effect has been achieved. This is a substantial
improvement over existing methods of administering drugs
through the mucosal tissues of the mouth.

15 The present invention also provides the advantage of
controlling the dissolution rate of the composition once it
is administered to a patient. This can be accomplished in
a number of ways. First, the dissolution rate may be
modified chemically by including a hydrophobic agent (such
20 as calcium stearate) to slow dissolution or lactose to
enhance dissolution. The solubility of the selected matrix
material, e.g., gelatin, fat, protein, wax, etc., likewise
affects the dissolution rate. Dissolution may also be
controlled by the extent to which the mixture is
25 mechanically compressed. In addition, dissolution can be
accomplished by varying the vigor with which the patient
sucks on the dissolvable matrix.

A drug administered through the oral mucosal tissues
from a dissolvable matrix within the scope of the present
30 invention will quickly enter the patient's bloodstream
through the veins which serve these tissues. Appropriate
monitoring of the patient's reaction to the drugs which
have an observable or monitorable effect (such as a drug
affecting the central nervous, cardiovascular, or renal
35

1 vascular systems) will indicate when the drug has evoked a
suitable response. The dosage-form may then be removed, or
its rate of consumption may be modified in order to
maintain the desired effect.

5 It will be appreciated that the ever present risk of
overdosing a patient is substantially minimized through the
use of the present invention. According to the present
invention, the drug dose is given over a period of time
rather than all at once, and the administration rate can be
10 adjusted if it appears to be necessary. Once a sufficient
drug response has been achieved, the patient can simply
stop sucking on the dosage-form or the patient or medical
professional can easily remove the dosage-form from the
patient's mouth.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of a mold for forming
the dissolvable drug matrix along with an associated ram.

20 Figure 2 is a perspective view of one embodiment of a
dosage-form within the scope of the present invention.

Figure 3 is an exploded plan view of the embodiment of
the dosage-form shown in Figure 2.

Figure 4 is a perspective view of an alternative
embodiment of the dosage-form of the present invention.

25 Figure 5 is a cutaway plan view of an alternative
embodiment of a dosage-form of the present invention
illustrating one method of attachment of the handle to the
dissolvable matrix.

30 Figure 6 is a perspective view of mold for forming a
dissolvable drug matrix which uses horizontal compression.

Figure 7 is a perspective view of the mold shown in
Figure 6 in the process of forming a dosage-form within the
scope of the present invention.

35

1 Figure 8 is a perspective view of the mold shown in
Figure 6 with the bottom die pushing a completed dosage-
form out of the mold.

5 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

1. General Discussion

 The present invention is related to methods of
manufacture and compositions which facilitate the
10 transmucosal delivery of a medication. Simply stated, the
present invention relates to a dosage-form, or similar type
of composition, which contains a therapeutic drug. The
drug is delivered to the patient through the mucosal
tissues of the mouth, pharynx, and esophagus as the patient
15 sucks on the drug-containing dosage-form.

 This particular method of delivery overcomes several
of the limitations encountered in the delivery of drugs
either orally or by injection. One of the primary
advantages of the present invention is the ability to
20 introduce drugs to a patient in a "dose-to-effect" manner.
The drug is given to the patient until the precisely
desired effect is obtained; this is in distinction to prior
art methods where a predetermined quantity of the drug is
introduced to the patient. Once the desired effect is
25 obtained, the patient or the medical professional simply
removes the dosage-form from the patient's mouth.

 The present invention discloses a method of producing
a dosage-form containing one or more therapeutic agents.
The present invention overcomes many of the problems
30 encountered generally in incorporating drugs into a
dissolvable matrix. For example, the present invention
teaches the mixing of solid powders or liquids at room
temperature, as opposed to liquid components at elevated
temperatures. The degradation of drugs, which often occurs
35

1 at the elevated temperatures needed to produce a molten
candy mass, is thereby avoided. This facilitates use of
drugs having relatively low melting points, or those drugs
which can experience decomposition below their melting
5 points. The mixing can also be done at very low temper-
atures. In this way, evaporation of any volatile ingred-
ients is minimized and the "stickiness" of sticky
ingredients is reduced making them more crumbly.

10 In addition, because solid powders or liquids are
combined together, constituents which may be chemically
incompatible when in a heated solution or suspension can be
mixed. In forming medicated confections by known methods,
severe problems are encountered in that the medication,
flavorings, and other components may be insoluble when
15 placed in the same liquid environment. In addition,
problems of chemical incompatibility between ingredients is
eliminated in the present invention.

Once the desired constituents are thoroughly mixed,
they may be formed into a solid dosage-form. In other
20 cases the constituents are wetted to form a slurry, dried,
and then compressed (sometimes referred to as "slugging").
In one embodiment, the ingredients are compressed to form
the dosage-form. Typically, compressive forces in the
range from approximately 2,000 Newtons to approximately
25 5,000 Newtons are preferred. As a result, the compressed
powdered matrix is held together by physical means rather
than by chemical means. The extent of the compressive
forces can be modified to vary the rate that the dosage-
form will dissolve in a patient's mouth. The greater the
30 compressive forces that form the mixture, the slower the
dissolution of the matrix material in the mouth.

In other embodiments within the scope of the present
invention, the desired constituents are formed into the
dosage-form by dehydration, freeze drying (lyophilization),

1 pouring into a mold, spraying onto a suitable holder, vapor
deposition, or other known techniques in the art.

According to the present invention, the dissolvable
matrix composition is attached to a holder or handle.
5 Attaching the dissolvable matrix to a holder facilitates
the administering of precise dosages. Once a particular
effect is induced, the dosage-form can be withdrawn using
the holder as described above.

The attachment of the dissolvable matrix material to
10 a holder may be made by incorporating the holder into the
dissolvable matrix as the dosage-form is being formed.
Alternatively, the holder may be glued, compressed,
screwed, snapped, or otherwise attached to the dissolvable
matrix once the matrix is formed. A dosage-form may be
15 assembled immediately prior to use by sliding disks of drug
and dissolvable matrix onto an appropriately configured
holder. Also, the dissolvable matrix may be sprayed or
otherwise deposited onto a handle during formation. In
addition, the dissolvable matrix may be formed around an
20 insert onto which a holder can be attached.

It will be appreciated that compression or attachment
of the drug-containing matrix onto a holder can facilitate
the transmucosal absorption of a variety of therapeutic
agents. Attachment to a holder also facilitates verifiable
25 transfer of the medication to the patient. The holder
provides a convenient point of reference concerning
quantities of drug administered at any particular point in
time; it is easy to determine how much of the dosage-form
has been dissolved in the patient's mouth.

30 Localization of effects by some therapeutic agents
such as local anesthetic agents, antiplaque agents, local
antipruritic agents, local antisecretory agents, and local
antifungal agents can also be accomplished according to the
present invention. Immediate systemic effects from central

1 nervous system-acting drugs (such as sedation, anxiolysis,
analgesia, amnesia, and anesthesia), cardiovascular-acting
agents (such as antihypertensives and antianginal drugs),
5 renal vascular-acting agents, and numerous other
therapeutic agents can also be accomplished by employing
the present invention.

Placing a drug dosage onto a holder also facilitates
the temporary removal of medication for inspection or the
reduction of the effect when necessary. Unlike
10 administration of drugs orally or even sublingually, the
present composition can easily be removed to assess the
effect induced at any particular time. When a pill or
lozenge is used, removal from the patient's mouth at an
intermediate stage to assess effect is generally imprac-
15 tical, if not impossible.

Dissolvable matrixes attached to a holder can also
avoid aspiration of the confection. One major problem with
existing lozenges and the like is their tendency to
crumble. Once the lozenge crumbles, controlled trans-
20 mucosal delivery is less ideal.

The present invention provides the capability of
providing a good tasting medication. With many drugs, it
has previously been extremely difficult to provide a good
tasting medicine because of the extreme bitterness or other
25 unpleasant taste of many drugs. Using the present
invention, favorable taste characteristics can be
accomplished by adding various flavors, sweeteners, and the
like to form an ideal mix of products. Since the compon-
ents are combined as solids or liquids (or even liquids
30 that are slowly released from microsponges), problems
associated with combining flavoring components insoluble in
a molten candy mass are avoided.

It is important to note that it is possible, according
to the present invention, to use the free acid form or the
35

1 free base form of certain drugs and to buffer those drugs
such that extremes in pH, and resulting bad taste, are
avoided.

5 Another important feature of the present invention is
the incorporation of permeation enhancers within the
dissolvable matrix. The permeation enhancers improve the
mucosal membrane permeability to lipophilic and nonlipo-
philic drugs. Thus, the compositions and methods within
10 the scope of the present invention permit the use of lipo-
philic as well as nonlipophilic drugs.

2. Methods of Manufacture

In order to prepare a desirable drug-containing
dissolvable matrix for formation into a dosage-form, it is
15 generally necessary to combine several general types of
components. These components include the types of
components used to prepare typical confections, the desired
drug, and other chemically active ingredients such as
buffering agents, permeation enhancers, and the like. The
20 types of components involved generally fall into the
following categories:

- (1) flavorings,
- (2) sweeteners,
- (3) flavor enhancers,
- 25 (4) releasing agents,
- (5) buffers,
- (6) one or more therapeutic agents,
- (7) dissolvable matrix material, and
- (8) permeation enhancers.

30 The components may be a releasable or slowly releasable
liquid.

As mentioned above, it is preferred that these
components each be provided in a form which facilitates
mixing, such as a dry powder. This provides for convenient

1 combination of the ingredients, even if they happen to be
insoluble or otherwise chemically incompatible. All the
incipients or inactive ingredients should be on the GRAS
list ("generally regarded as safe").

5 A wide range of flavors are available for preparing
good tasting and desirable medications within the scope of
the present invention. These are required in order to mask
the unpleasant taste of the drug. Flavorings may be
combined, as desired, to produce a particular flavor mix
10 which is compatible with a particular medication. Some of
the confectioner's flavorings which have been used in the
context of the present invention include artificial
vanilla, vanilla cream, mint, cherry, spearmint, grape,
coconut, chocolate, menthol, licorice, lemon, and
15 butterscotch.

Each of these flavorings is obtainable in a
concentrated powder form. Other flavorings known in the
confectionery arts may also be acceptable because of the
ease of combining the ingredients of the present invention.
20 Any number of flavorings may be combined in any desired
ratio in order to produce the specific desired taste
characteristics required for any particular application.
For example, flavor combinations may be varied in order to
be compatible with the flavor characteristics of any
25 specific drug.

In order to produce a desirable color for the end
product, artificial colorings may also be added to the
composition. The flavorings described above are generally
a white powder, as are the other major components.
30 Therefore, additional coloring is necessary if a colored
end product is desired. Coloring may also be important as
a code to indicate the type and concentration of drug
contained within a particular dissolvable matrix. Any type

1 of color known to be "FD&C" certified may be used to provide coloring to the product.

2 In order to provide a good tasting medication, it is
3 necessary to add sweeteners to the composition. Sweeteners
4 which are presently preferred include aspartame
5 (NutraSweet®) and compressible confectioner's sugar. Other
6 sweeteners, such as fructose, sorbitol, mannitol, xylitol,
7 cyclamates, acesulfame K, thaumatin, sucralose, alitame,
8 PS99/PS100, glycyrrhizin, monellin, stevioside, miraculin,
9 or L-sugars may also be acceptable for use within the scope
10 of the present invention. Again, it is desired that a
11 sweetener or combination of sweeteners be obtained which is
12 compatible with the drug and the other components such that
13 a good tasting confection is produced.

14 Maltodextrin and cyclodextran may also be added to
15 provide a better tasting composition. Maltodextrin and
16 cyclodextran are generally employed in order to dissipate
17 unpleasant flavors (such as the bitter taste of most drugs)
18 within the composition. In addition, maltodextrin is a
19 highly compressible powder which facilitates the formation
20 of compressible dosage-forms within the scope of the
21 present invention.

22 For some applications, it may be desirable to add a
23 flavor enhancer to the composition in order to achieve a
24 good tasting product. Flavor enhancers provide a more
25 pleasant sensation in the patient's mouth during
26 consumption of the dosage-form. Flavor enhancers within
27 the scope of the present invention include materials such
28 as ribotide (a nucleotide) and monosodium glutamate
29 ("msg").
30

31 In certain medications, it may also be desirable to
32 add a lubricating agent in order to release the dosage-form
33 from the mold. Such agents may also provide a certain
34 amount of waterproofing. As mentioned above, the rate of
35

1 dissolution of the dosage-form within the patient's mouth
may be controlled chemically, as well as physically,
through the extent of compression of the composition.
These lubricating or releasing agents may include
5 substances such as compritol 888 (glyceryl behenate),
calcium stearate, and sodium stearate. These agents may
enhance dissolution or they may inhibit dissolution as
necessary.

Lubricating agents are also useful in those embod-
10 iments wherein a powder mixture is funneled into a chute
during manufacture. Lubricating agents and surfactants
improve product flow and avoid static electricity charge
buildup within the formulation which may cause the
ingredients to separate due to electrostatic forces.

15 As will be discussed in more detail below, it may also
be desirable to include buffering agents within the
composition. Buffering agents provide the ability to place
the medication in the mouth in a favorable pH environment
for passage across the mucosal tissues of the mouth,
20 pharynx, and esophagus. Buffering agents incorporated
within the composition can be used to affect a pH change in
the salival environment of the mouth in order to favor the
existence of a unionized form of the active ingredient or
drug which more readily moves through the mucosal tissues.

25 In addition, appropriate pH adjustment can aid in
producing a more palatable product with drugs which are
either severely acidic (and thus sour) or severely basic
(and thus bitter). As a result, a buffer system such as
citric acid/sodium citrate has been found to be desirable
30 for addition into the dissolvable matrix. A phosphate
buffer system may also be used.

A suitable permeation enhancer capable of improving
the drug permeability across the mucosal membrane may also
be included in the dissolvable composition. Permeation

1 enhancers are particularly important when nonlipophilic
drugs are used, but may be valuable for lipophilic drugs as
well. Examples of typical permeation enhancers which may
5 be used within the scope of the present invention are
discussed below.

It will be appreciated that miscellaneous other agents
such as lactose, to provide filling and bulk, may also be
desirable. Other filling and bulking agents of the type
known in the art may also be used. Gelatin may be used to
10 provide filling and bulking agents in other embodiments of
the present invention.

Added to the dissolvable matrix described above will
be the appropriate therapeutic agent or drug. As will be
discussed in more detail below, various types of drugs are
15 easily incorporated into the matrix compositions of the
present invention. These include agents which affect the
central nervous system, the cardiovascular system, or the
renal vascular system.

A typical dosage-form within the scope of the present
20 invention may include the following general ingredients:
flavoring, sweetener, flavor enhancer, releasing agent,
buffer, therapeutic agent(s), and/or bulk dissolvable
matrix. The "bulk dissolvable matrix" may include
hydrogel-, gelatin-, fat-, protein-, wax-based, and other
25 similar dissolvable substances. Appropriate changes in
flavoring ingredients can be made to mask or optimize
flavor perception in order to achieve ultimate acceptance
of the dosage-form by the desired patient group, be it
adult, juvenile, pediatric, or neonate.

30 Each of the components is mixed with the other
components to produce the compositions of the present
invention. It is presently preferred to use the method of
geometric dilution in mixing the various components. Using
this method, the two smallest ingredients by weight (as a

1 proportion of the final product) are first mixed together
thoroughly.

When complete mixing has been obtained between those
two components, the next smallest ingredient or ingredients
5 by weight equal to the weight of the previous ingredients
is added and mixed thoroughly with the existing mixture.
This procedure is repeated until all of the components are
added to the mix and mixed thoroughly with all other
components.

10 Geometric dilution provides for complete and thorough
mixing of all of the components. Using the method
described above, there is little chance for incomplete
mixing and uneven distribution of components throughout the
mix. It will be recognized that this is an advancement
15 over the art in that existing methods may result in
incomplete mixing because of the insolubility of the
products.

Once complete mixing is accomplished, the mixture is
formed into a solid dissolvable matrix composition. In one
20 embodiment, the mixture is compressed under relatively high
forces to provide a coherent dosage. Compressive forces in
the range of from approximately 2,000 Newtons to
approximately 5,000 Newtons are presently preferred,
however, any force which is sufficient to compress the
25 ingredients into a coherent, integrated mass could be used.

In other embodiments within the scope of the present
invention, the desired constituents are formed into the
dosage-form by dehydration, freeze drying (lyophilization),
pouring into a mold, spraying onto a suitable holder, vapor
30 deposition, or other known techniques in the art.

When employing the present invention, there is no need
to heat the mixture to a molten mass as has been the
practice in the past in forming drug-containing
confections. As a result, heat degradation of the drug
35

1 component is avoided while good mixing and a uniform product are provided.

5 The dissolvable matrix may be attached to a holder such as a handle or other similar type of holder. The holder may be glued to the matrix by dissolvable adhesive such as confectioner's glue, liquid sorbitol, or wax. Alternatively, the holder may be compressed or molded into the dissolvable matrix as described above.

10 The figures illustrate several methods of forming the dosage-form, as well as methods of attaching the holder to the dosage-form. Figure 1 discloses a mold block 10. The interior of mold block 10 includes a cavity 12 formed in any desired shape so that the ingredients described above can be compressed or molded to form an appropriately shaped dosage. Mold block 10 may comprise two separate halves 14 and 16. Each half of the mold block 10 can be removed in order to remove the dosage-form once it is formed.

Also illustrated in Figure 1 is ram 18. Ram 18 is configured so that it fits into the cavity 12 and compresses the dosage-form into the base of cavity 12. Ram 18 may have a hole disposed through its interior in order to accommodate handle 20. Thus, handle 20 can be placed into the mass of dosage-form prior to compression. Ram 18 will then compress the dosage-form tightly around handle 20. Following compression of the dosage-form, the handle is securely bound in place.

Figure 2 discloses an additional embodiment of the dosage-form of the present invention. The dosage-form illustrated in Figure 2 has alternating layers of dissolvable matrix 22 and a drug matrix 24. Each alternating segment is disk-shaped with the width of the disk being varied according to particular needs. Disks 22 and 24 easily slide over handle 26 and seat against button 28. Thus, the method of assembly of the dosage-form can be

1 adapted to produce various dosages to fit varying
circumstances. Indeed, the patient himself may be capable
of assembling an appropriate dosage-form and varying the
content of the medicament to correspond to his specific
5 needs at any particular time.

Figure 3 illustrates the method of assembling the
embodiment of the invention as illustrated in Figure 2. In
Figure 3, the drug matrix 24 and dissolvable matrix 22 are
spaced apart along handle 26. As can be appreciated from
10 Figure 3, disks 22 and 24 will slide onto handle 26 and
will seat against button 28. The number of disks and the
composition of these disks can be easily varied to meet
particular patient needs. Various concentrations of a
drug, or even multiple drugs, may be administered in this
15 manner.

Handle 26 may take various shapes. For example, it
may be desirable for handle 26 to be oval or triangular in
cross section. This would prevent disks 24 and 26 from
turning on the handle. In addition, an additional sleeve
20 (not shown) may be positioned over the exposed portion of
the handle with a catch that engages handle 26 so that
disks 24 and 26 are locked in place.

Figure 4 illustrates a further embodiment of a dosage-
form within the scope of the present invention. In Figure
25 4, the drug and dissolvable matrix are divided laterally
along the cylindrical mass of the dosage-form. Thus, pie-
shaped segments of drug 32 and dissolvable matrix material
34 are pressed together around handle 30. As illustrated
in Figure 4, drug segments 32 and dissolvable segments 34
30 may alternate around a periphery of the dosage-form.
Alternatively, the spacing of the segments may be varied to
provide other appropriate levels of drug dosage.

Figure 5 illustrates an alternate method of attachment
between the dosage-form 36 and the handle 38. Handle 38
35

1 illustrated in Figure 5 is constructed with a plurality of
protrusions 40. Protrusions 40 extend toward the exposed
portion of the handle such that they prevent the dosage-
5 form 36 from sliding off the handle. Thus, when the dosage-
form 36 is compressed around handle 38, the dosage-form is
securely bound to the handle.

Figures 6-8 illustrate a mold block 50 for forming a
dosage-form within the scope of the present invention.
Mold block 50 defines an die cavity 52. A slot 54, located
10 on one edge of mold block 50 facilitates insertion and
removal of holder 56. A top die 58 and a bottom die 60 are
configured to be inserted within die cavity 52. The top
and bottom die both have concave surfaces 62 and 64,
respectively.

15 To prepare a dosage-form using mold block 50, a
quantity of dissolvable matrix material which contains the
medicament is placed in die cavity 52 on concave surface
64. A holder 56 is positioned within slot 54 such that a
portion of the holder is within the die cavity. An
20 additional amount of dissolvable matrix material is placed
in the die cavity on top of the holder. The top and bottom
dies then compress the dissolvable matrix material around
the holder thereby preparing a dosage-form 68. In order to
remove the dosage-form from the mold block, the bottom die
25 pushes the completed dosage-form out of the die cavity as
shown in Figure 8.

It can be seen, therefore, that the present invention
provides a great deal of flexibility in the construction of
an appropriate drug-containing confection. The quantity of
30 drug contained in any confection can be varied within wide
ranges. In addition, various methods of attachment of the
confection to the handle are available in order to provide
a wide range of flexibility.

1 3. Control of pH in View of Drug pKa

 It is well known that most drugs are weak acids or
weak bases and are present in solution in both the
unionized and ionized forms. It has been found that the
unionized portion of the drug is usually lipid soluble and
can readily diffuse across the cell membrane. The ionized
portion, conversely, is often lipid insoluble and in some
instances, may not effectively penetrate the lipid membrane
of the cell. As a result, drugs in the ionized form are
generally inefficient in producing a drug effect on the
central nervous, cardiovascular, and renal vascular
systems.

 Whether a drug exists in the ionized or unionized form
is largely dependent upon its pKa, and correspondingly on
the pH of the solution. The present invention provides the
unique ability to control the pH of the solution and thus
the ratio of unionized to ionized form of the drug.

 Ingredients of the dissolvable matrix or other dosage-
form can be designed to impart sufficient change in the pH
of the saliva within the mouth such that the concentration
of the unionized drug is increased. When the percentage of
unionized drug is increased, transmucosal absorption of the
drug is correspondingly increased. Therefore, by
influencing the salival pH environment, it is possible to
greatly improve the extent and rapidity of actual drug
absorption, and therefore, the initial onset of the effect
of the drug. Adding pH buffering systems (such as
phosphate or citrate buffer systems) into the dosage-form
can greatly facilitate delivery of the drug in the
unionized (lipid soluble) form.

 It is often desirable for the pKa to range from
approximately 5 to approximately 8 in order to maximize
drug delivery. pKa is defined as the negative logarithm
(base 10) of the dissociation constant (Ka). pKa may also

1 be defined as the pH at which a given acid is 50% ionized
and 50% unionized. The term pKb is used when referring to
a base. pKa and pKb can be calculated from pH, if the
5 concentrations of the charged and uncharged species are
known, using the well-known Henderson-Hasselbach equation
if concentrations of the charged and uncharged species are
known. The Henderson-Hasselbach equation is as follows:

$$\begin{aligned} 10 \quad \text{pKb} &= \text{pH} + \log \left| \frac{\text{charged}}{\text{uncharged}} \right| && \text{for bases} \\ \text{pKa} &= \text{pH} + \log \left| \frac{\text{uncharged}}{\text{charged}} \right| && \text{for acids} \end{aligned}$$

From these equations, the unionized portion of the drug
will be increased by lowering the pH for weak acid drugs
15 and increasing the pH for weak base drugs.

The effect on the pKa of varying pH, and thus on the
unionized drug available, is extremely dramatic. For
example, sodium methohexital (the salt of a weak acid), a
potent central nervous system-acting drug, has a pKa of
20 7.9. If at the same time the general pH of the saliva is
about 7.5, these values can then be placed in the
Henderson-Hasselbach equation as follows:

$$25 \quad 7.9 = 7.5 + \log (X)$$

where X is the ratio of the unionized to the ionized drug
form. Solving this calculation indicates that under
typical conditions in the mouth, 72% of the methohexital
available would exist in the unionized form. As was
30 mentioned above, the unionized drug form is the primary
form that is transported across the lipid cell membrane.

In the event that the salival pH is buffered down to
approximately 6.7, the ratio of unionized to ionized drug
changes dramatically. This results in a corresponding
35

1 dramatic change in the amount of drug available. Under
these conditions, 94% of the drug available exists in the
unionized form.

5 Comparing the ratio of unionized to ionized drug
produced under the two sets of pH conditions described
above, it can be seen that dramatic changes occur.
Changing the pH from 7.5 to 6.7 produces a substantial
improvement in the concentration of unionized drug
10 available for delivery across the lipid membrane. This
results directly in a dramatic improvement in drug delivery
across the cell membranes in the mouth and a corresponding
increase in the effectiveness of the drug administered.

Changes in pH such as those discussed above can be
accomplished by incorporating particular buffer systems
15 within the confection composition. One presently preferred
buffer system is a citric acid/sodium citrate system;
however, other conventional buffers (such as phosphate) may
also be used. By using such a buffer, dramatically better
results may be achieved such that buccal drug absorption is
20 a fully feasible and optimal delivery method.

It will be appreciated that an additional advantage
of the change of the pH may be that the taste character-
istics of the drug can be improved. Drugs which are very
high in pH typically are very bitter in taste. As the pH
25 drops, the taste becomes less bitter, then salty, and may
eventually become sour. Flavorings can more adequately
improve the taste characteristics of drugs in the lower pH
ranges. As a result, in addition to improving the drug
delivery, buffering pH may also improve the taste charact-
30 eristics of the composition. Although the foregoing
discussion has focused on the alteration of pH to enhance
drug permeability by increasing the percentage of unionized
drug forms, pH may enhance drug permeability by unknown
mechanisms. For example, pH may affect drug molecular

1 configuration which enhances drug permeability. Nonetheless, drug pH is often an important consideration in drug
administration.

5 4. Mucosal Membrane Permeation Enhancers

As discussed above, most drugs are present in solution in both the unionized and ionized forms. Generally only lipid soluble or lipophilic drugs readily
10 diffuse across mucosal membranes. However, it has been found that nonlipophilic drugs may diffuse across mucosal membranes if the mucosal membrane is treated with a permeation enhancer. It has also been found that certain permeability enhancers can significantly enhance the permeability of lipophilic and nonlipophilic drugs.

15 Typical permeation enhancers may include bile salts such as sodium cholate, sodium glycocholate, sodium glycodeoxycholate, taurodeoxycholate, sodium deoxycholate, sodium lithocholate chenocholate, chenodeoxycholate, ursocholate, ursodeoxycholate, hydrodeoxycholate,
20 dehydrocholate, glycochenocholate, taurochenocholate, and taurochenodeoxycholate. Other permeation enhancers such as sodium dodecyl sulfate ("SDS"), dimethyl sulfoxide ("DMSO"), sodium lauryl sulfate, salts and other derivatives of saturated and unsaturated fatty acids,
25 surfactants, bile salt analogs, derivatives of bile salts, or such synthetic permeation enhancers may also be used.

It is almost impossible to predict which enhancer will work best for a given drug. For each individual drug, only experiments can tell which enhancer is the most
30 suitable. However, it is generally believed that bile salts are good enhancers for hydrophilic drugs and long chain fatty acids, their salts, derivatives, and analogs are more suitable for lipophilic drugs. DMSO, SDS, and medium chain fatty acids (C-8 to about C-14) their salts,

1 derivatives, and analogs may work for both hydrophilic and
lipophilic drugs.

5 The effectiveness of some enhancers may vary depend-
ing on the chemical compound to be permeated. One partic-
ular enhancer may work very well on one drug but may not
have any effect on another drug. For example, oleic acid
greatly improves the transdermal permeability of estradiol,
a very lipophilic drug, but oleic acid does not have any
effect on the transmucosal permeability of glucose, a very
10 hydrophilic drug. Although it is possible to speculate
whether a given enhancer may or may not enhance a given
drug's permeability, the actual effectiveness of an
enhancer should be verified experimentally.

15 The permeation enhancer concentration within the
dissolvable matrix material may be varied depending on the
potency of the enhancer and rate of dissolution of the dis-
solvable matrix. Other criteria for determining the
enhancer concentration include the potency of the drug and
the desired lag time. The upper limit for enhancer concen-
20 tration is set by toxic effect to or irritation limits of
the mucosal membrane.

The following is a list of typical enhancers and an
exemplary concentration range for each enhancer:

25

30

35

1	<u>Enhancer</u>	<u>Operational Concentration</u>	<u>Preferred Range</u>
	sodium cholate	0.02% - 50%	0.1% -16%
5	sodium dodecyl sulfate	0.02% - 50%	0.1% -2%
	sodium deoxycholate	0.02% - 50%	0.1% -16%
	taurodeoxycholate	0.02% - solubility	0.1% -16%
	sodium glycocholate	0.02% - solubility	0.1% -16%
10	sodium taurocholate	0.02% - solubility	0.1% -16%
	DMSO	0.02% - solubility	5% -50%

5. Suitable Therapeutic Agents

15 In order for the present invention to operate effectively, it is necessary that the therapeutic agent incorporated within the dissolvable matrix be capable of permeating the mucosal membrane either alone or by suitable adjustments in the environmental pH, or other chemical modification or in combination with a suitable permeation
20 enhancer. In some embodiments, the therapeutic agent may be microencapsulated or incorporated into microsponges.

The present invention has applicability to a variety of drugs affecting the central nervous system. For example, the present invention may easily be utilized in
25 the administration of opioid agonists (such as fentanyl, alfentanil, sufentanil, lofentanil, and carfentanil), opioid antagonists (such as naloxone and nalbuphene), butyrophenones (such as droperidol and haloperidol); benzodiazepines (such as valium, midazolam, triazolam,
30 oxazolam, and lorazepam); GABA stimulators (such as etomidate); barbiturates (such as Thiopental, methohexital, thiamazol, pentobarbital, and hexabarbital); di-isopropylphenols drugs (such as diprivan); and other

1 central nervous system-acting drugs such as levodopa. It
 will be appreciated that other drugs may also be utilized
 within the scope of the present invention either singly or
 in combination.

5 Table 1 lists some of the CNS-acting drugs which are
 suitable for incorporation into the dosage-form of the
 present invention, as well as some of the characteristics
 of those drugs.

TABLE 1

10	<u>GENERIC DRUG</u>	<u>DRUG CLASS</u>	<u>DOSE RANGE</u>
	methohexital	barbiturate	10-500 mg
	pentobarbital	barbiturate	50-200 mg
	thiamylal	barbiturate	10-500 mg
	thiopental	barbiturate	50-500 mg
15	fentanyl	opioid agonist	0.05-5 mg
	alfentanil	opioid agonist	0.5-50 mg
	sufentanil	opioid agonist	5-500 μ g
	lofentanil	opioid agonist	0.1-100 μ g
	carfentanil	opioid agonist	0.2-100 μ g
20	naloxone	opioid antagonist	0.05-5 mg
	nalbuphene	opioid antagonist	1-50 mg
	diazepam	benzodiazepine	1-40 mg
	lorazepam	benzodiazepine	1-4 mg
	midazolam	benzodiazepine	0.5-25 mg
25	oxazepam	benzodiazepine	5-40 mg
	triazolam	benzodiazepine	250-1000 mg
	droperidol	buterophenone	1-20 mg
	haloperidol	buterophenone	0.5-10 mg
	propanidid	eugenol	1-10 mg
30	etomidate	GABA stimulator	5-60 mg
	propofol	substituted phenol	3-50 mg
	ketamine	phencyclidine	5-300 mg
	diprivan	substituted phenol	5-20 mg

1 Drugs having effects on the cardiovascular and renal
 vascular systems may also be administered using a dosage-
 form of the present invention. A few examples of such
 drugs are identified in Table 2.

5

TABLE 2

	<u>GENERIC DRUG</u>	<u>DRUG CLASS</u>	<u>DOSE RANGE</u>
	Bretylium	antiarrhythmic	50-500 mg
	Captopril	ACE inhibitor	25-75 mg
10	Clonidine	antihypertensive	0.1-0.5 mg
	Dopamine	renal vascular	0.5-5 mg
	Enalapril	ACE inhibitor	5-15 mg
	Esmolol	antihypertensive/angina	100-250 mg
	Furosemide	diuretic	20-100 mg
15	Isosorbide	angina	2.5-40 mg
	Labetolol	antihypertensive	100-400 mg
	Lidocaine	antiarrhythmic	50-250 mg
	Metolazone	diuretic	5-50 mg
	Metoprolol	antihypertensive	25-100 mg
20	Nadolol	antihypertensive	40-160 mg
	Nifedipine	antihypertensive/ angina/vasodilator	10-40 mg
	Nitroglycerin	antihypertensive/angina	0.4-1.0 mg
	Nitroprusside	hypotensive	10-50 mg
25	Propranolol	antihypertensive/angina	0.1-50 mg

In addition to the foregoing, there are many other
 drugs which can be administered using a dosage-form of the
 present invention. Exemplary of such drugs are those
 30 identified in Table 3.

1	<u>Table 3</u>		
	<u>GENERIC DRUG</u>	<u>DRUG CLASS</u>	<u>DOSE RANGE</u>
	Benzquinamide	antiemetic	25-100 mg
	Meclizine	antiemetic	25-100 mg
5	Metoclopramide	antiemetic	5-20 mg
	Prochlorperazine	antiemetic	5-25 mg
	Trimethobenzamide	antiemetic	100-2500 mg
	Clotrimazole	antifungal	10-20 mg
10	Nystatin	antifungal	100,000-500,000 units
	Carbidopa	antiparkinson with levodopa	10-50 mg
	Levodopa	antiparkinson	100-750 mg
	Sucralfate	antisecretory	1-2 grams
15	Albuterol	bronchodilator	0.8-1.6 mg
	Aminophylline	bronchodilator	100-500 mg
	Beclomethasone	bronchodilator	20-50 µg
	Dyphylline	bronchodilator	100-400 mg
	Epinephrine	bronchodilator	200-500 µg
20	Flunisolide	bronchodilator	25-50 µg
	Isoetharine	bronchodilator	170-680 µg
	Isoproterenol HCl	bronchodilator	60-260 µg
	Metaproterenol	bronchodilator	0.65-10 mg
	Oxtriphylline	bronchodilator	50-400 mg
25	Terbutaline	bronchodilator	2.5-10 mg
	Theophylline	bronchodilator	50-400 mg
	Ergotamine	antimigraine	2-4 mg
	Methysergide	antimigraine	2-4 mg
	Propranolol	antimigraine	80-160 mg
30	Suloctidil	antimigraine	200-300 mg
	Ergonovine	oxytocic	0.2-0.6 mg
	Oxytocin	oxytocic	5-20 units
	Desmopressinacetate	antidiuretic	10-50 µg
	Lypressin	antidiuretic	7-14 µg

1	Vasopressin	antidiuretic	2.5-60 units
	Insulin	antihyperglycemic	1-100 units

5 In addition to the foregoing drugs, certain
macromolecular drugs (such as β -endorphin, enkephalins,
bradykinin, aniotensin I, gonadotropic hormones, adreno-
corticotropic hormone (ACTH), calcitonin, parathyroid
hormone, and growth hormone), polysaccharides (such as
10 heparin), antigens, antibodies, and enzymes may be adapted
for transmucosal administration within the scope of the
present invention.

When incorporating a drug into a dissolvable matrix
within the scope of the present invention, the amount of
drug used will generally differ from the amount used in
15 more traditional injection and oral administration
techniques. Depending upon the lipophilic nature of the
drug, its potency, the use of permeation enhancers, and the
drug's end use, the total concentration of the drug in the
typical dosage-form may contain up to 50 times more than
20 the amount of drug which would typically be used in an
injection, but it may also contain significantly less than
the amount used orally, and it may also contain less than
the amount used in some intramuscular injections. For
purposes of example, Tables 1, 2, and 3 set forth presently
25 contemplated ranges of the dosages of certain drugs which
could be typically used.

A wide variety of drugs may be used within the scope
of the present invention. The present invention allows
drugs to be incorporated within the dissolvable matrix
30 which would otherwise be insoluble, unpleasant tasting, or
have other undesirable characteristics. This capability is
provided by the various formation techniques of the dosage-
form. The present invention also allows both lipophilic as

1 well as nonlipophilic drugs to be utilized depending on the
use of permeation enhancers.

As was mentioned above, methohexital is one presently
preferred drug for use in the dissolvable dosage-form of
5 the present invention. Tests were run in which
methohexital dosage-forms were given to six volunteers.
The dosage-forms each contained 500 milligrams of
methohexital. Each patient experienced the sedative
effects of the drug in a matter of minutes after beginning
10 to suck on the dosage-form. These tests indicated that the
dosage-form of the present invention is effective in
administering methohexital in a dose-to-effect manner.

Using the methohexital dosage-form described above,
it was possible to produce either mild or heavy sedation or
15 induce anesthesia. By removing the dosage-form when the
ideal degree of sedation was achieved, it was possible to
gradually increase sedation to the desired level.

In addition, the results show that the use of oral
transmucosal methohexital significantly decreases the drug
20 dosage required to produce optimal sedation when compared
to rectal administration. The dosage was reduced from
between 25 and 30 mg/kg when methohexital is administered
rectally to between 6 and 8 mg/kg methohexital is given by
way of the oral transmucosal dosage-form. The use of an
25 enhancer may reduce this dosage even more.

In summary, it will be appreciated that a wide
variety of drugs can be used within the scope of the
present invention. At the same time, several benefits are
provided. Efficient delivery of the drug is facilitated
30 while at the same time drug degradation is avoided. The
drug can also be administered in a dose-to-effect manner so
that the drug effect produced is precisely controlled.

1

5. Examples of the Present Invention

The following examples are given to illustrate various embodiments which have been made or may be made in accordance with the present invention. These examples are given by way of example only, and it is to be understood that the following examples are not comprehensive or exhaustive of the many types of embodiments of the present invention which can be prepared in accordance with the present invention.

Example 1

In this example, methohexital was incorporated into a dissolvable matrix form. Methohexital is a known potent lipophilic drug useful as an anxiolytic, sedative and for anesthetizing a patient. Its high potency and lipophilicity makes it an excellent drug for transmucosal administration in accordance with the present invention.

A suitable mixture was prepared by combining the following ingredients as follows:

	<u>Ingredient</u>	<u>%</u>	<u>grams</u>
	citric acid	1%	0.2
	ribotide	2%	0.4
	compritol 888	2%	0.4
25	aspartame	2%	0.4
	vanilla microcaps	5%	1.0
	vanilla cream microcaps	5%	1.0
	wild cherry microcaps	3%	0.6
	peppermint microcaps	3%	0.6
30	compressible sugar	20%	4.0
	methohexital sodium	25%	5.0
	maltodextrin	<u>32%</u>	<u>6.4</u>
		100%	20

35

1 The ingredients were combined in a mixer in such a
fashion as to ensure a uniform distribution of all
ingredients within the mixture. Aliquots of 2 grams each
were then hydraulically compressed around a commercially
5 available wax-coated compressed paper holder, using a force
sufficient to provide a final volume of 2 cubic centi-
meters. The procedure resulted in the preparation of 10
oral transmucosal dosage-forms, each containing 0.5 grams
of methohexital.

10

Example 2

In this example, methohexital was incorporated into
a dissolvable matrix form. Gelatin was selected as the
dissolvable matrix material. Methohexital is a known
15 potent lipophilic drug useful as an anxiolytic, sedative
and for anesthetizing a patient. Its high potency and
lipophilicity makes it an excellent drug for transmucosal
administration in accordance with the present invention.

A suitable mixture was prepared by combining the
20 following ingredients as follows:

	<u>Ingredient</u>	<u>%</u>	<u>grams</u>
	citric acid	1%	0.2
	ribotide	2%	0.4
25	compritol 888	2%	0.4
	aspartame	2%	0.4
	vanilla microcaps	5%	1.0
	vanilla cream microcaps	5%	1.0
	wild cherry microcaps	3%	0.6
30	peppermint microcaps	3%	0.6
	methohexital sodium	25%	5.0
	gelatin	<u>52%</u>	<u>10.4</u>
		100%	20

35

1 The ingredients were combined in a mixer in such a
fashion as to ensure a uniform distribution of all
ingredients within the mixture. Aliquots of 2 grams each
were then formed by dehydration. The procedure resulted in
5 the preparation of 10 oral transmucosal dosage-forms, each
containing 0.5 grams of methohexital.

 It will be appreciated that similar dosage-forms may
be produced using other dissolvable matrix materials such
as fats, waxes (natural or synthetic), proteins, hydrogels,
10 dissolvable resins, or other suitable dissolvable matrix
materials.

6. Summary

 In summary, the present invention provides
15 compositions and methods of manufacture for administering
a drug in a precise dose in order to obtain a rapid effect.
In addition, the present invention provides methods for
forming a drug containing dissolvable matrix having the
following attributes:

- 20 (1) drugs having relatively low melting points
can be used without degrading the drug;
 (2) drugs that are volatile can be incorporated
into the matrix;
 (3) disagreeable flavor characteristics can be
25 masked;
 (4) insoluble ingredients can be used;
 (5) chemically incompatible ingredients can be
used;
 (6) buffer forming reagents can be added to
30 optimize the ratio of ionized and nonionized drug
form;
 (7) chemical agents can be added to modify the
dissolution characteristics of the drug;

1 (8) permeation enhancers can be added to
increase the drug absorption;

 (9) lipid soluble mixtures can be added to
increase drug absorption;

5 (10) dissolution characteristics can be modified
mechanically by changing the compressive forces used
to form the dissolvable matrix;

 (11) stratification of active ingredients can be
accomplished;

10 (12) the dosage can be modified by utilizing an
assembly of dosage units onto a holder; and

 (13) both lipophilic and nonlipophilic drugs can
be suitably used.

 The present invention, therefore, provides the
15 ability to provide precise control over the dosage and
effect of the drug. This is obtained by transmucosal
administration of the drug by sucking a drug-containing
dissolvable dosage-form having a handle. As a result, the
precise dosage and effect can be obtained.

20 The present invention may be embodied in other
specific forms without departing from its spirit or
essential characteristics. The described embodiments are
to be considered in all respects only as illustrative and
not restrictive. The scope of the invention is, therefore,
25 indicated by the appended claims rather than by the
foregoing description. All changes which come within the
meaning and range of equivalency of the claims are to be
embraced within their scope.

 What is claimed is:

30

35

1 1. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient, said
composition comprising:

a soluble matrix material;

5 a pharmacologically effective dose of a potent
drug being capable of absorption through mucosal
tissues of the mouth, pharynx, and esophagus and
being dispersed throughout the matrix material and
formed into a substantially solid integral mass which
10 is capable of dissolving in the mouth of the patient
so that the drug is released for absorption through
mucosal tissues of the mouth, pharynx, and esophagus
upon dissolution of the integral mass in the mouth of
the patient;

15 buffer forming reagents dispersed throughout the
integral mass, the buffer forming reagents being
capable of modifying the salival pH when dissolved in
saliva such that a majority of the drug remains
unionized in order to facilitate transmucosal
20 absorption of the drug; and

holder means secured to the integral mass so as
to form a drug-containing dosage-form, the holder
means being configured so as to permit convenient
insertion and removal of the drug-containing integral
25 mass into and out of the mouth of the patient.

2. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the soluble matrix material comprises
30 a soluble carbohydrate material.

1 3. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the soluble matrix material comprises
a soluble fat material.

5 4. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the soluble matrix material comprises
a soluble protein material.

10 5. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the soluble matrix material comprises
a soluble wax material.

15 6. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the soluble matrix material comprises
a soluble hydrocarbon material.

20 7. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 2, wherein the soluble carbohydrate material
comprises a solidified molten matrix.

25 8. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 2, wherein the soluble carbohydrate material
comprises a compressed powder.

30 9. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 8, wherein the drug incorporated into the
compressed powder matrix is microencapsulated.

35

1

10. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 8, wherein the drug incorporated into the compressed powder matrix is included within a microsphere.

11. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 2, wherein the soluble carbohydrate material comprises a hydrogel.

12. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 2, wherein the soluble carbohydrate material comprises a gelatin.

13. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the drug is dispersed substantially uniformly throughout the matrix material.

14. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the drug is dispersed in circular layers throughout the matrix material.

15. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the buffer forming reagents comprise a citrate buffer system.

1 16. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the buffer forming reagents comprise a
phosphate buffer system.

5

 17. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the drug-containing integral mass
further includes a lubricating agent dispersed
10 substantially uniformly throughout the integral mass in
order to aid in the manufacture of the drug-containing
dosage-form.

 18. A drug-containing dosage-form for use in
15 transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the drug-containing integral mass
further includes a surfactant dispersed substantially
uniformly throughout the integral mass in order to aid in
the manufacture of the drug-containing dosage-form.

20

 19. A drug-containing composition for use in
transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the drug-containing integral mass
further includes maltodextrin dispersed substantially
25 uniformly throughout the integral mass in order to aid in
dissipating any unpleasant flavors of the drug in the
integral mass.

 20. A drug-containing dosage-form for use in
30 transmucosal delivery of the drug to a patient as defined
in claim 1, wherein the drug-containing dosage-form
integral mass further includes at least one flavor enhancer
dispersed substantially uniformly throughout the integral
mass.

35

1

21. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the drug-containing integral mass
5 further includes a substantially water-insoluble component dispersed substantially uniformly throughout the integral mass in order to make slower the dissolution of the integral mass in the mouth of the patient.

10

22. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the potent drug is substantially lipophilic.

15

23. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 1, wherein the potent drug is substantially nonlipophilic.

20

25

30

35

1 24. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient, said
dosage-form comprising:

a soluble matrix material;

5 a pharmacologically effective dose of a potent
drug being capable of absorption through mucosal
tissues of the mouth, pharynx, and esophagus and
being dispersed throughout the matrix material and
formed into a substantially solid integral mass which
10 is capable of dissolving in the mouth of the patient
so that the drug is released for absorption through
mucosal tissues of the mouth, pharynx, and esophagus
upon dissolution of the integral mass in the mouth of
the patient;

15 a permeation enhancer which is also dispersed
throughout the integral mass, the permeation enhancer
being capable of modifying the permeability of the
mucosal tissues of the mouth, pharynx, and esophagus
towards the drug in order to facilitate transmucosal
20 absorption of the drug; and

holder means secured to the integral mass so as
to form a drug-containing dosage-form, the holder
means being configured so as to permit convenient
insertion and removal of the drug-containing integral
25 mass into and out of the mouth of the patient.

25 25. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the permeation enhancer is not
30 dispersed uniformly throughout the integral mass.

1 26. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 25, wherein a more of the permeation enhancer is
5 dispersed about the outer periphery of the dosage-form than
in the center portion of the dosage-form.

 27. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the drug is dispersed substantially
10 uniformly throughout the matrix material.

 28. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble matrix material comprises
15 a soluble carbohydrate material.

 29. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble matrix material comprises
20 a soluble fat material.

 30. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble matrix material comprises
25 a soluble protein material.

 31. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble matrix material comprises
30 a soluble wax material.

1 32. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble matrix material comprises
a soluble hydrocarbon material.

5 33. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble carbohydrate material
comprises a solidified molten matrix.

10 34. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the soluble carbohydrate material
comprises a compressed powder.

15 35. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 34, wherein the drug incorporated into the
compressed powder matrix is microencapsulated.

20 36. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 34, wherein the drug incorporated into the
compressed powder matrix is included within a microsphere.

25 37. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 28, wherein the soluble carbohydrate material
comprises a hydrogel.

30 38. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 28, wherein the soluble carbohydrate material
comprises a gelatin.

35

1

39. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 24, wherein the permeation enhancer comprises a bile salt.

40. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 24, wherein the permeation enhancer comprises a synthetic permeation enhancer.

41. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 24, wherein the drug-containing integral mass further includes a lubricating agent dispersed substantially uniformly throughout the integral mass in order to aid in the manufacture of the drug-containing dosage-form.

42. A drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 24, wherein the drug-containing integral mass further includes a surfactant dispersed substantially uniformly throughout the integral mass in order to aid in the manufacture of the drug-containing dosage-form.

43. A drug-containing composition for use in transmucosal delivery of the drug to a patient as defined in claim 24, wherein the drug-containing integral mass further includes maltodextrin dispersed substantially uniformly throughout the integral mass in order to aid in dissipating any unpleasant flavors of the drug in the integral mass.

35

1 44. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the drug-containing integral mass
further includes at least one flavor enhancer dispersed
5 substantially uniformly throughout the integral mass.

 45. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the drug-containing integral mass
10 further includes a substantially water-insoluble component
dispersed substantially uniformly throughout the integral
mass in order to make slower the dissolution of the
integral mass in the mouth of the patient.

15 46. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the potent drug is substantially
lipophilic.

20 47. A drug-containing dosage-form for use in
transmucosal delivery of the drug to a patient as defined
in claim 24, wherein the potent drug is substantially
nonlipophilic.

25

30

35

1 48. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient, the method comprising the steps of:

5 (a) obtaining a pharmacologically effective
dose of a potent drug capable of absorption through
mucosal tissues of the mouth, pharynx, and esophagus;

 (b) obtaining a soluble matrix material capable
of dissolving within the mouth of the patient;

10 (c) mixing the drug and the matrix material to
form a drug-containing matrix such that the drug is
dispersed throughout the drug-containing matrix;

 (d) dispersing a buffer forming reagent
throughout the integral mass, the buffer forming
reagent being capable of modifying the salival pH
15 when dissolved in saliva such that a majority of the
drug remains unionized in order to facilitate
transmucosal absorption of the drug;

 (e) forming a substantially solid integral mass
from the drug-containing matrix which is capable of
20 dissolving in the mouth of the patient so that the
drug is released for absorption through mucosal
tissues of the mouth, pharynx, and esophagus upon
dissolution of the integral mass in the mouth of the
patient; and

25 (f) incorporating a holder as part of the
integral mass in order to form the drug-containing
dosage-form.

 49. A method for producing a drug-containing dosage-
30 form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the buffer forming
reagent comprises a citrate buffer system.

1 50. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the buffer forming
reagent comprises a phosphate buffer system.

5

 51. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the holder is
incorporated into the integral mass by compression of the
10 drug-containing matrix around the holder during forming
step (e).

 52. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
15 patient as defined in claim 48 wherein the holder is
incorporated as part of the integral mass by affixing the
holder to the integral mass after forming step (e).

 53. A method for producing a drug-containing dosage-
20 form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug-containing
matrix includes at least one flavor enhancer.

 54. A method for producing a drug-containing dosage-
25 form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug-containing
matrix includes maltodextrin in order to aid in dissipating
any unpleasant flavors of the drug.

30

35

1 55. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein a substantially
water-insoluble component is added to the drug-containing
5 matrix such that the dissolution of the integral mass in
the mouth of the patient is made slower by the
substantially water-insoluble component in the drug-
containing matrix.

10 56. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug is
substantially lipophilic.

15 57. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug is
substantially nonlipophilic.

20 58. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug is
methohexital.

25 59. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug is
fentanyl.

30 60. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug is selected
from the group consisting of triazolan, oxazepam,
lorazepam, etomidate, and thiamylal.

35

1

61. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug is
5 nitroglycerin.

62. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug is selected
10 from the group consisting of isosorbide dinitrate, captopril, nifedipine, clonidine, and esimolol.

63. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a
15 patient as defined in claim 48 wherein the drug is a potent, fast-acting drug.

64. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a
20 patient as defined in claim 48 wherein the drug has effects on the central nervous system of the patient.

65. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a
25 patient as defined in claim 48 wherein the drug has effects on the cardiovascular system of the patient.

66. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a
30 patient as defined in claim 48 wherein the drug has effects in the renal vascular system of the patient.

35

1 67. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has effects
in the respiratory system of the patient.

5 68. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has
antiemetic effects on the patient.

10 69. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has
antifungal effects on the patient.

15 70. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has
antiparkinson effects on the patient.

20 71. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has
antisecretory effects on the patient.

25 72. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has
antimigraine effects on the patient.

30 73. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 48 wherein the drug has
oxytotic effects on the patient.

35

1

74. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug has
5 antidiuretic effects on the patient.

75. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug has anti-
10 hyperglycemic effects on the patient.

76. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug has opioid
15 agonist effects on the patient.

77. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug has opioid
20 antagonist effects on the patient.

78. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein the drug has
25 diuretic effects on the patient.

79. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 48 wherein drug is dispersed
30 substantially uniformly throughout the matrix material.

1 80. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient, the method comprising the steps of:

5 (a) obtaining a pharmacologically effective
dose of a potent drug capable of absorption through
mucosal tissues of the mouth, pharynx, and esophagus;

 (b) obtaining a soluble matrix material capable
of dissolving within the mouth of the patient;

10 (c) mixing the drug and the matrix material to
form a drug-containing matrix such that the drug is
dispersed throughout the drug-containing matrix;

 (d) dispersing a permeation enhancer throughout
the integral mass, the permeation enhancer being
capable of modifying the permeability of the mucosal
15 tissues of the mouth, pharynx, and esophagus towards
the drug in order to facilitate transmucosal
absorption of the drug;

 (e) forming a substantially solid integral mass
from the drug-containing matrix which is capable of
20 dissolving in the mouth of the patient so that the
drug is released for absorption through mucosal
tissues of the mouth, pharynx, and esophagus upon
dissolution of the integral mass in the mouth of the
patient; and

25 (f) incorporating a holder as part of the
integral mass in order to form the drug-containing
dosage-form.

 81. A method for producing a drug-containing dosage-
30 form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the permeation
enhancer is not dispersed uniformly throughout the integral
mass.

1 82. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein a higher
concentration of the permeation enhancer is dispersed about
5 the outer periphery of the dosage-form than in the center
portion of the dosage-form.

 83. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
10 patient as defined in claim 80, wherein the potent drug is
dispersed substantially uniformly throughout the matrix
material.

 84. A method for producing a drug-containing dosage-
15 form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the permeation
enhancer comprises a bile salt.

 85. A method for producing a drug-containing dosage-
20 form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the permeation
enhancer comprises a synthetic permeation enhancer.

 86. A method for producing a drug-containing dosage-
25 form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the drug possesses
sufficient nonlipophilic properties such that a permeation
enhancer is needed to enable the drug to be absorbed
through the mucosal tissue.

30

35

1 87. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the holder is
5 incorporated into the integral mass by compression of the
drug-containing matrix around the holder during forming
step (e).

 88. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
10 patient as defined in claim 80, wherein the holder is
incorporated as part of the integral mass by affixing the
holder to the integral mass after forming step (e).

 89. A method for producing a drug-containing dosage-
15 form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the drug-containing
matrix includes at least one flavor enhancer.

 90. A method for producing a drug-containing dosage-
20 form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the drug-containing
matrix includes maltodextrin in order to aid in dissipating
any unpleasant flavors of the drug.

25 91. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein a substantially
water-insoluble component is added to the drug-containing
matrix such that the dissolution of the integral mass in
30 the mouth of the patient is made slower by the
substantially water-insoluble component in the drug-
containing matrix.

1 92. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80 wherein the drug is
substantially lipophilic.

5

 93. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80 wherein the drug is
substantially nonlipophilic.

10

 94. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80 wherein the drug has opioid
agonist effects on the patient.

15

 95. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80 wherein the drug has opioid
antagonist effects on the patient.

20

 96. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the drug is a
potent, fast-acting drug.

25

 97. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the drug has
effects on the central nervous system of the patient.

30

 98. A method for producing a drug-containing dosage-
form for use in transmucosal delivery of the drug to a
patient as defined in claim 80, wherein the drug has
effects on the cardiovascular system of the patient.

35

1

99. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 80, wherein the drug has
5 effects in the renal vascular system of the patient.

100. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 80, wherein the drug has
10 effects respiratory system of the patient.

101. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a patient as defined in claim 80, wherein the permeation
15 enhancer comprises a lipid soluble supplement which acts as a permeation enhancer.

102. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a
20 patient as defined in claim 80, wherein the drug-containing matrix comprises a sweetener.

103. A method for producing a drug-containing dosage-form for use in transmucosal delivery of the drug to a
25 patient as defined in claim 102, wherein the sweetner is an artificial sweetner.

30

35

1/3

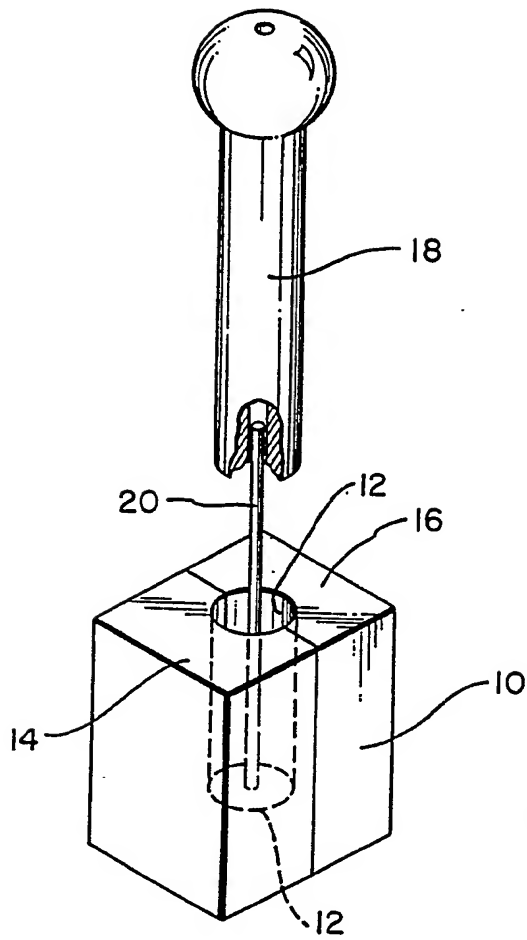


FIG. 1

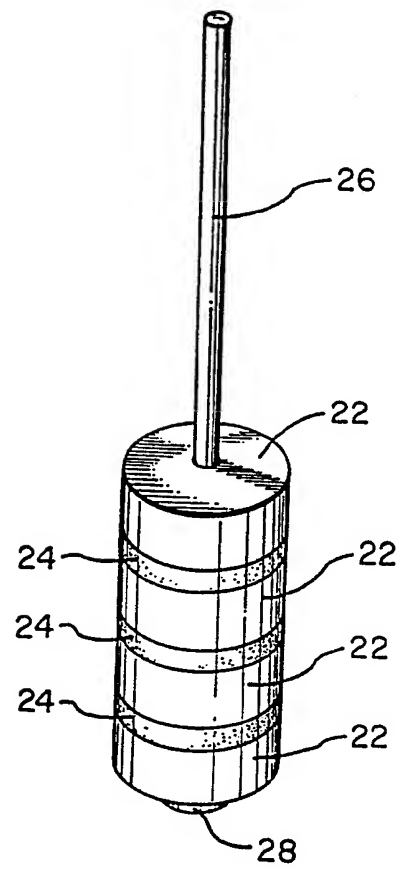


FIG. 2

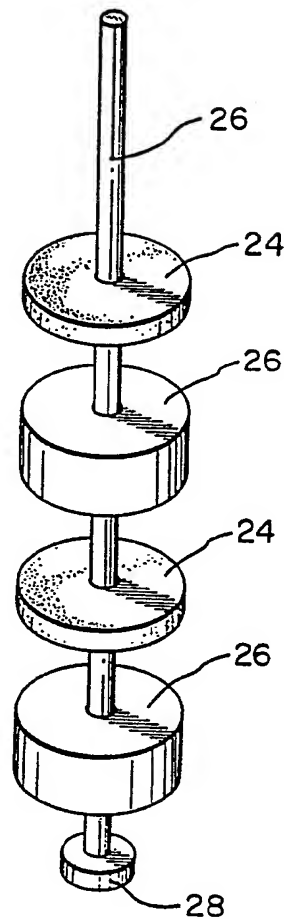


FIG. 3

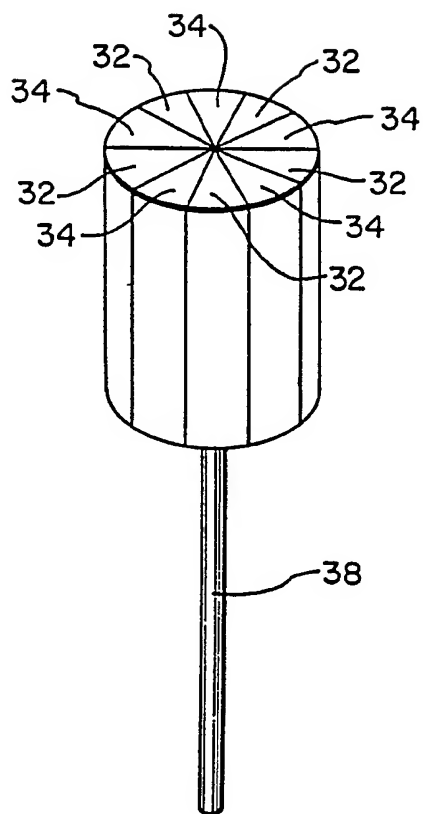


FIG. 4

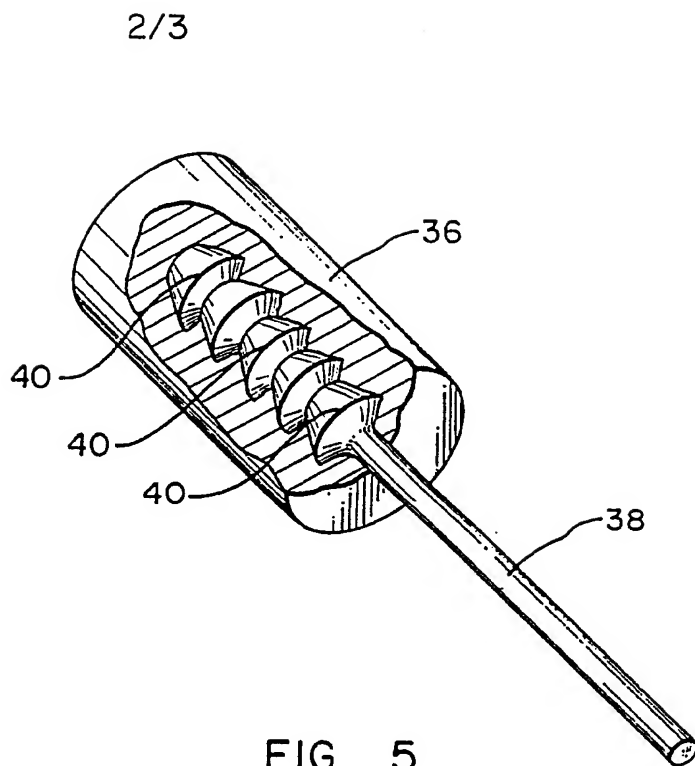


FIG. 5

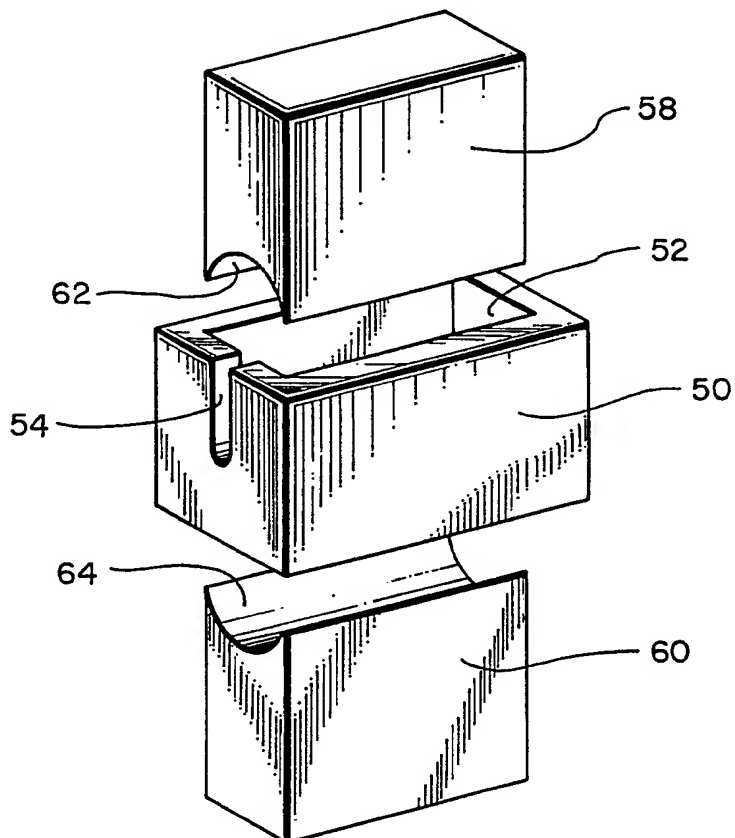


FIG. 6

3/3

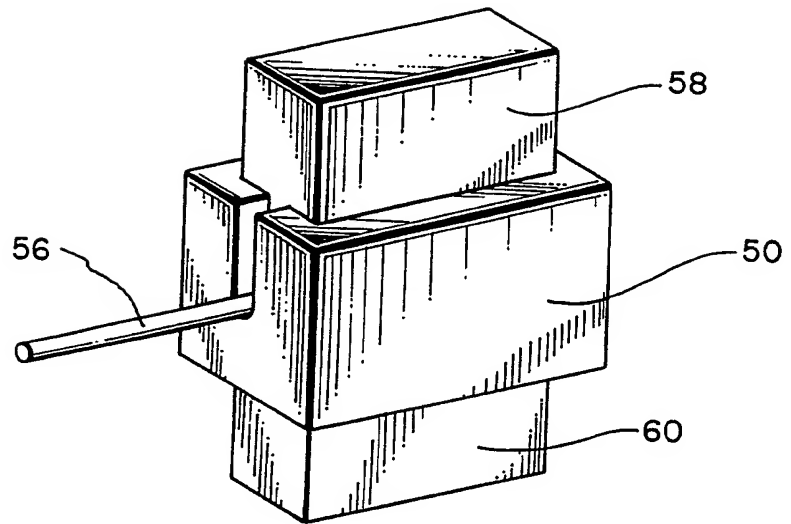


FIG. 7

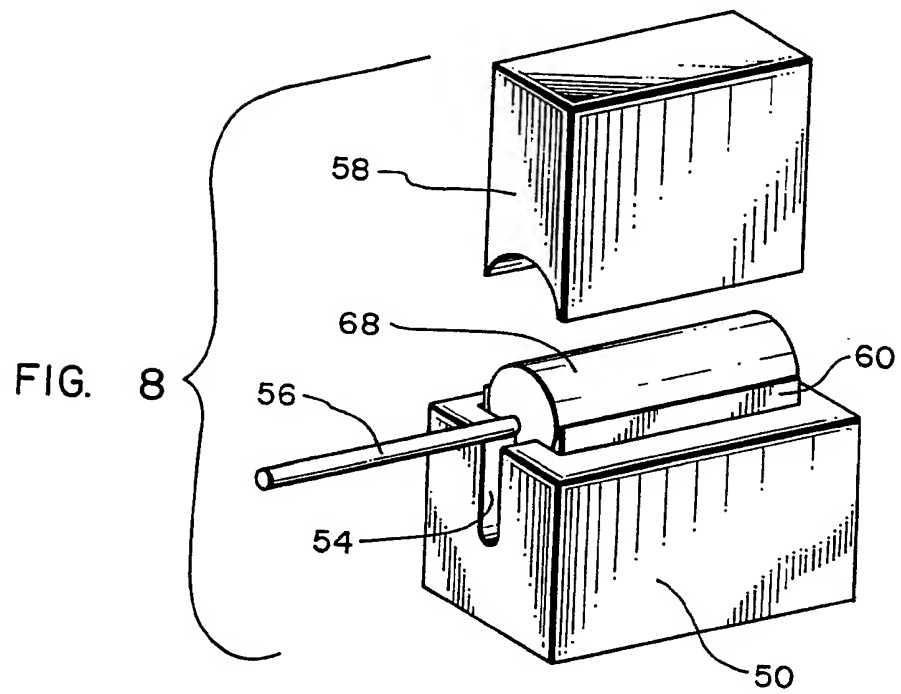


FIG. 8

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/04384

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC (5): A61K 9/68 U.S. CL. 424/440																										
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched ⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; padding: 5px;">Classification System</th> <th style="padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; padding: 10px;">U.S.</td> <td style="text-align: center; padding: 10px;">424/439, 440, 441</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	U.S.	424/439, 440, 441																				
Classification System	Classification Symbols																									
U.S.	424/439, 440, 441																									
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; padding: 5px;">Category [*]</th> <th style="width: 70%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 122,507 (WILLS) 02 JANUARY 1872 See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 2,963,404 (HAMMER) 06 DECEMBER 1960 See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 3,556,811 (SMITH) 19 JANUARY 1971 See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 3,622,352 (DAYLOR, JR.) 23 NOVEMBER 1971; See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 3,697,641 (AHRENS) 10 OCTOBER 1972 See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 4,551,329 (HARRIS) 05 NOVEMBER 1985 See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> <tr> <td style="text-align: center; padding: 10px;">A</td> <td style="padding: 10px;">US, A, 4,642,231 (PETERS) 10 FEBRUARY 1987 See entire document.</td> <td style="text-align: center; padding: 10px;">1-103</td> </tr> </table> <div style="margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> </div>			Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	US, A, 122,507 (WILLS) 02 JANUARY 1872 See entire document.	1-103	A	US, A, 2,963,404 (HAMMER) 06 DECEMBER 1960 See entire document.	1-103	A	US, A, 3,556,811 (SMITH) 19 JANUARY 1971 See entire document.	1-103	A	US, A, 3,622,352 (DAYLOR, JR.) 23 NOVEMBER 1971; See entire document.	1-103	A	US, A, 3,697,641 (AHRENS) 10 OCTOBER 1972 See entire document.	1-103	A	US, A, 4,551,329 (HARRIS) 05 NOVEMBER 1985 See entire document.	1-103	A	US, A, 4,642,231 (PETERS) 10 FEBRUARY 1987 See entire document.	1-103
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³																								
A	US, A, 122,507 (WILLS) 02 JANUARY 1872 See entire document.	1-103																								
A	US, A, 2,963,404 (HAMMER) 06 DECEMBER 1960 See entire document.	1-103																								
A	US, A, 3,556,811 (SMITH) 19 JANUARY 1971 See entire document.	1-103																								
A	US, A, 3,622,352 (DAYLOR, JR.) 23 NOVEMBER 1971; See entire document.	1-103																								
A	US, A, 3,697,641 (AHRENS) 10 OCTOBER 1972 See entire document.	1-103																								
A	US, A, 4,551,329 (HARRIS) 05 NOVEMBER 1985 See entire document.	1-103																								
A	US, A, 4,642,231 (PETERS) 10 FEBRUARY 1987 See entire document.	1-103																								
IV. CERTIFICATION <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> Date of the Actual Completion of the International Search <div style="text-align: center; font-size: 1.2em;">26 SEPTEMBER 1990</div> </td> <td style="width: 50%; vertical-align: top;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.5em;">18 JAN 1991</div> </td> </tr> <tr> <td style="vertical-align: top;"> International Searching Authority <div style="text-align: center;">ISA/US</div> </td> <td style="vertical-align: top;"> Signature of Authorized Officer <div style="text-align: center;">T.K. Page <i>TK Page</i></div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; font-size: 1.2em;">26 SEPTEMBER 1990</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.5em;">18 JAN 1991</div>	International Searching Authority <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer <div style="text-align: center;">T.K. Page <i>TK Page</i></div>																				
Date of the Actual Completion of the International Search <div style="text-align: center; font-size: 1.2em;">26 SEPTEMBER 1990</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-size: 1.5em;">18 JAN 1991</div>																									
International Searching Authority <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer <div style="text-align: center;">T.K. Page <i>TK Page</i></div>																									